Remarks

We note with appreciation the withdrawal from the novelty rejection under 35 U.S.C. §102 and the objections and rejections based on form.

Claims 2-9, 24, 25 and 45-49 are present in the case. Claims 2 and 24 have been amended to correct minor typographical errors. Claim 46 has been amended to add "β1," as supported at page 3 of the Specification. No new matter has been added.

Turning to the prior art, we respectfully submit that none of the cited references precludes patentability of the solicited claims for the reasons detailed hereinafter.

Claim 2 encompasses a chimeric protein heterodimer complex comprising a chimeric protein of an α-chain of an integrin and a heavy or light chain of an immunoglobulin and a chimeric protein of a β-chain of an integrin and a heavy or light chain of an immunoglobulin. Claims 3-9 depend from Claim 2. Claims 45 and 46 are directed to a chimeric protein comprising an α-chain of an integrin selected from α1, α2, α3, α4, α5, α6, α7, α8, α9, αv, αL, αM, α11b, and αE or a β-chain of an integrin selected from β1, ß2, ß3, ß4, ß5, ß6, ß7 and ß8 and a heavy or light chain of an immunoglobulin. Claims 47-49 are drawn to chimeric proteins of SEQ ID NO: 1, SEQ ID NO: 19, or SEQ ID NO: 2, respectively. Claims 24 and 25 relate to a drug or drug composition comprising the chimeric proteins or chimeric protein heterodimer complexes.

We respectfully submit that the invention is patentably distinct over Carter and Hori. When applying 35 U.S.C. §103, the prior art must be considered as a whole and must suggest the desirability and, thus, the obviousness of making the combination. The "as a whole" requirement mandates consideration of portions of the prior art that would lead away from the invention. *See* W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 U.S.P.Q 303 (Fed. Cir. 1983). Furthermore, "[t]o support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why

the artisan would have found the claimed invention to have been obvious in light of the teachings of that reference." Ex parte Clapp, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985). Moreover, a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *See* In re Geisler, 43 U.S.P.Q.2d 1362,1366 (Fed. Cir. 1997).

The "art-recognized uses" of adhesion molecule/Ig fusion proteins taught by Carter in addition to the fact that integrins are adhesion molecules has been cited as the motivation to combine Carter and Hori. When considered in its entirety, however, Carter does not provide one of ordinary skill in the art with motivation to look to Hori. Hori, in fact, teaches away from any such hypothetical combination.

Carter teaches a method by which a single host cell is transformed with nucleic acid constructs encoding polypeptide components of a multimer which are coexpressed to allow multimer formation (Col. 25). Specifically, Carter teaches construction of an immunoadhesin molecule containing the binding domain of an adhesin molecule fused to the hinge and F_c regions of an immunoglobulin heavy chain and suggests that the immunoadhesins may be assembled within the host cell as multimers (Column 19). We agree, however, that Carter fails to teach that the adhesin molecule is an integrin subunit.

In sharp contrast to Carter, Hori discloses a method according to which each of two cells is engineered to express one component of a multimeric protein followed by fusion of the two cells to allow multimer formation (Column 5). While Hori teaches that the multimeric protein may be an integrin, Hori does not teach the use of a chimeric protein between an integrin and an immunoglobulin. Furthermore, Hori does not teach the use of a chimeric protein heterodimer complex which comprises a chimeric protein comprising an α chain of an integrin and a heavy chain or light chain of an immunoglobulin and a chimeric protein comprising of a β chain of an integrin and a heavy chain or light chain of an immunoglobulin. The primary objective of the method of Hori is to avoid co-

transformation of the DNA constructs into a single cell as performed in Carter. As noted at Columns 3 and 4 of Hori, the cell fusion method taught therein provides distinct advantages over the co-expression method of Carter: cells expressing a single component of the final multi-component protein can be individually selected and the final multicomponent protein is not expressed until all cells expressing the individual components of the multicomponent protein are fused into a single hybrid cell. Thus, Hori specifically teaches that the method of Carter is unsatisfactory to achieve the objectives of Hori. As such, one of ordinary skill would not look to Hori on the basis of the disclosure of Carter as those references teach wholly incongruent methods. As Hori teaches away from a hypothetical combination with Carter, we respectfully submit that an obviousness rejection based on such a combination is improper.

Furthermore, neither Carter nor Hori teaches or suggests a chimeric protein having a sequence corresponding to SEQ ID NO: 1, SEQ ID NO: 19, or SEQ ID NO: 2, or a chimeric protein heterodimer complex containing such a protein, as claimed in Claims 7-9 and 47-49. Careful scrutiny of both disclosures reveals no SEQ ID NO: 1, no SEQ ID NO: 19 and no SEQ ID NO: 2. Thus, we respectfully submit that no *prima facie* case of obviousness has been established on this record as to those claims.

We further respectfully submit that the prior art listed in the Specification at pages 2-3 fail to even mention a chimeric protein containing an integrin subunit fused to a heavy or light chain of an immunoglobulin or a heterodimer complex containing such a chimeric protein. Thus, we respectfully submit that the solicited claims are patentably distinct over those references.

Turning to Gallatin, in sharp contrast to the invention as defined by Claims 24, 25, and 45-49, Gallatin teaches only a fusion protein of amino acids 17 to 1108 of the α_d subunit of an integrin to a human immunoglobulin constant domain (Claim 19). As Gallatin fails to teach a chimeric protein of a full-length α-subunit or β-subunit to a full-length heavy or

light chain of an immunoglobulin as presently claimed in Claims 45 and 46, no motivation to combine Gallatin with the prior art disclosed at pages 2-3 of the Specification existed at the time of the invention. Gallatin further fails to teach or suggest fusion proteins having SEQ ID NO: 1, SEQ ID NO: 19, or SEQ ID NO: 2, as in Claims 47-49. Since Gallatin fails to teach or suggest the chimeric proteins of Claims 45-49, we respectfully submit that Claims 24, 25 and 45-49 are patentably distinguishable over that reference.

Applicants have developed a new and useful invention relating to chimeric proteins of integrin subunits and immunoglobulin heavy or light chains with significant diagnostic and therapeutic applications. We respectfully submit that Claims 2-9, 24, 25 and 45-49 are in proper form for allowance, which early action is hereby requested.

Respectfully submitted,

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